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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,383	08/01/2003	Milton Hammerly		2828

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EXAMINER	
WILLIAMS, LEONARD M	
ART UNIT	PAPER NUMBER
1617	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/633,383	HAMMERLY, MILTON	
	Examiner	Art Unit	
	Leonard M. Williams	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/1/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Election/Restrictions

The examiner has considered the response to the species requirement received 11/6/2006 and has found it persuasive. Thus the election of species requirement is herby withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clay et al. (US Patent No. 5843984), in view of Safe (US Patent No. 5948808) and further in view of Michnovicz et al. (Changes in Levels of Urinary Estrogen Metabolites After Oral Indole-3-Carbinol Treatment in Humans, Journal of the National Cancer Institute, May 21 1997, Vol. 89, No. 10, pp. 718-723).

Clay et al. teach, in col. 4 line 50 to col. 5 line 32, compounds of formula I (sulfonated derivatives of Raloxifene, a known antiestrogen) or a pharmaceutically acceptable salt or solvate thereof, for use in pharmaceutical compositions optionally containing estrogen or progestin, and the use of said compounds either alone or in combination with estrogen or progestin, for alleviating symptoms of post-menopausal syndrome, particularly osteoporosis, cardiovascular related pathological conditions, and estrogen-dependent cancer. By estrogen, Clay et al. means steroidal compounds having estrogenic activity such as, 17-b-estradiol, estrone, conjugated estrogen (PremarinTM), equine estrogen, 17-b-ethynyl estradiol, and the like. In Table 1, Clay et al. demonstrate the antiestrogenic, uterine eosinophil infiltration, and serum cholesterol activity of the claimed compounds in comparison with 17-a-ethynyl estradiol and the

known antiestrogen Raloxifene. The activity of compounds 1a and 1b are statistically improved over the control compounds.

In col. 18 lines 10-45, Clay et al. teach that the compounds can be formulated as tablets, capsules, suspensions, powders, solutions and elixirs and can be administered via oral, parenteral, intramuscular, intravenous or subcutaneous routes. In Formulation 8, Clay et al. disclose a capsule containing the active ingredient (a compound of formula I) at 50mg, Premarin at 1mg, Avicel 50mg, starch1500 117.50mg, silicon oil 2mg, Tween 80 0.50mg, and Cab-o-sil at 0.25mg. In Formulation 10, Clay et al. disclose a combination tablet again containing 50mg of active agent and 1mg or Premarin.

Clay et al. does not disclose the use of a cruciferous indole compound (selected from indole 3-carbinol, diindolylmethane and derivatives thereof) in combination with an estrogenic substance, or the importance of the ratio of 2-hydroxylated estrogen metabolites to 16a-hydroxylated estrogen metabolites.

Safe et al. teaches in the abstract, compounds and compositions of substituted indole-3-carbinols and diindolylmethanes suitable for treating estrogen-dependent tumors. In col. 1 lines 30-65, Safe teaches that antiestrogens are chemicals which inhibit estrogens from eliciting their full response in target tissues and include the compound Tamoxifen. Further indole 3-carbinol (I3C) has been shown to inhibit the formation or growth of estrogen-regulated tumors in the rodent mammary, endometrium and uterus suggesting that I3C is an antiestrogen. In col. 2 lines 20 to col. 3 line 63, Safe discloses several indole-3-carbinol and diindolylmethane compounds for use as antiestrogens including 5-methyl-indole-3-carbinol, 5-ethyl-indole-3-carbinol, 5-propyl-

indole-3-carbinol, 5-butyl-indole-3-carbinol, 5-pentyl-indole-3-carbinol, 5-methoxy-indole-3-carbinol, 5-ethoxy-indole-3-carbinol, 5-propyloxy-indole-3-carbinol, 5-butyloxy-indole-3-carbinol, 5-amyloxy-indole-3-carbinol, N-methyl-indole-3-carbinol, N-ethyl-indole-3-carbinol, N-propyl-indole-3-carbinol, N-butyl-indole-3-carbinol, N-pentyl-indole-3-carbinol, 2-methyl-indole-3-carbinol, 2-ethyl-indole-3-carbinol, 2-propyl-indole-3-carbinol, 2-butyl-indole-3-carbinol and 2-pentyl-indole-3 –carbinol 5,5'-dichloro-diindolylmethane; 5,5'-dibromo-diindolylmethane; 5,5'-difluoro-diindolylmethane; 5,5'-dimethyl-diindolylmethane; 5,5'-diethyl-diindolylmethane; 5,5'-dipropyl-diindolylmethane; 5,5'-dibutyl-diindolylmethane; 5,5'-dipentyl-diindolylmethane; 5,5'-dimethoxy-diindolylmethane; 5,5'-diethoxy-diindolylmethane; 5,5'-dipropyloxy-diindolylmethane; 5,5'-dibutyloxy-diindolylmethane; 5,5'-diamyloxy-diindolylmethane; N, N'-dimethyl-diindolylmethane; N,N'-diethyl-diindolylmethane; N,N'-dipropyl-diindolylmethane; N,N'-dibutyl-diindolylmethane; N,N'-dipentyl-diindolylmethane; 2, 2'-dimethyl-diindolylmethane; 2,2'-diethyl-diindolylmethane; 2,2'-dipropyl-diindolylmethane; 2,2'-dibutyl-diindolylmethane and 2,2'-dipentyl-diindolylmethane.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the indole 3-carbinol and diindolylmethane antiestrogen compounds of Safe in the compositions of Clay et al. as Clay et al. teaches the use of an antiestrogen compound in conjunction with an estrogen and/or progestin for alleviating symptoms of post-menopausal syndrome, particularly osteoporosis, cardiovascular related pathological conditions, and estrogen-dependent cancer. Safe demonstrates that the indole 3-carbinol and diindolylmethane compounds are effective

antiestrogen compounds. One would expect a reasonable chance of success in achieving an equivalent therapeutic effect with the antiestrogen compounds of Safe in combination with estrogen and/or progestin as Clay et al. has demonstrated such efficacy with other antiestrogens.

Michnovicz et al. teach, on page 718, that in a study of the changes in levels of urinary estrogen metabolites after oral administration of indole-3-carbinol in humans it was found that I3C treatment resulted in increased urinary excretion of 2-hydroxylated estrogens and decreased urinary excretion of nearly all other estrogen metabolites including 16α-hydroxyestrone. On page 720, Michnovicz et al. teach that previous studies have indicated that 16α-estrogens such as 16α-hydroxyestrone retained estrogen activity and formed covalent bonds with proteins and generated DNA adducts in cell culture which indicative of mammary cell carcinogenesis. In contrast, the 2-estrogen metabolites have been shown to be weak estrogens or antiestrogens. On page 718 in the *Implications* section, Michnovicz et al. disclose that I3C may have chemopreventive activity against breast cancer in humans. One of ordinary skill in the art at the time the invention was made would have understood that maximizing the ratio of 2-hydroxyestrogens to 16-hydroxyestrogens in any estrogen based therapy would be important in order to minimize the possibilities of the development of breast cancer, as Michnovicz et al. have clearly linked the alteration of such estrogen metabolites as possible in humans, and have indicated that such alterations should be chemopreventive of breast cancer in humans.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leonard M. Williams whose telephone number is 571-272-0685. The examiner can normally be reached on MF 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LMW

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER